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REVIEW

Tumor Necrosis Factor–Neutralizing Therapies Improve Altered Hormone Axes

An Alternative Mode of Antiinflammatory Action

Rainer H. Straub,[1] Peter Härle,[1] Piercarlo Sarzi-Puttini,[2] and Maurizio Cutolo[3]

Introduction

In chronic inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis, Crohn's disease, and others, tumor necrosis factor (TNF) neutralization exerts positive disease-ameliorating effects (1–4). Although significant side effects of anti-TNF treatment have been reported (5), the use of anti-TNF strategies has greatly expanded our therapeutic arsenal and started a whole new area of drug development. In addition, TNF-neutralizing therapies have extended our understanding of the pathogenetic role of TNF and downstream molecules such as interleukin-6 (IL-6) in inflammatory diseases. TNF neutralization has strong direct antiinflammatory effects; however, such therapy may also support other important antiinflammatory pathways, such as the hypothalamic–pituitary–adrenal (HPA) axis, the hypothalamus–pituitary gland–liver–muscle axis, the hypothalamic–pituitary–gonadal (HPG) axis, and the hypothalamus–autonomic nervous system (HANS) axis. Normalization of the milieu interne would be an important favorable side effect.

In this review, we summarize the information regarding how TNF interferes with these neuroendocrine axes and how TNF neutralization improves some of these altered neuroendocrine pathways. From the present point of view, it seems obvious that blockade of TNF in chronic inflammatory diseases probably exerts indirect disease-ameliorating effects by restoring important neuroendocrine immune functions.

Loss of adrenal and gonadal androgens

Several independent groups of investigators have reported markedly decreased serum and urine levels of androgens such as dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), androstenedione, and testosterone in patients with RA (6–11). This finding is relevant, because androgens exert antiinflammatory effects in animal models of chronic inflammation and in patients with RA (for review, see ref. 12). It is thought that the loss of adrenal and gonadal androgens in patients with chronic inflammatory diseases supports continuation of the chronic inflammatory process.

The most important enzymatic step in a cell of adrenal and gonadal glands responsible for androgen production is the second step of the P450c17 reaction (Figure 1 and Table 1). TNF inhibits the reaction of this double enzyme step in human adrenocortical cells and in murine Leydig cells (Figure 1 or Table 1) (13,14). In patients with RA, neutralization of TNF leads to a significant increase in the level of androstenedione in

[1]Rainer H. Straub, MD, Peter Härle, MD: University Hospital Regensburg, Regensburg, Germany; [2]Piercarlo Sarzi-Puttini, MD: University Hospital L. Sacco, Milan, Italy; [3]Maurizio Cutolo, MD: University of Genoa, Genoa, Italy.

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Address correspondence and reprint requests to Rainer H. Straub, MD, Laboratory of Experimental Rheumatology and Neuroendocrino-Immunology, Division of Rheumatology, Department of Internal Medicine I, University Hospital, 93042 Regensburg, Germany. E-mail: rainer.straub@klinik.uni-regensburg.de.

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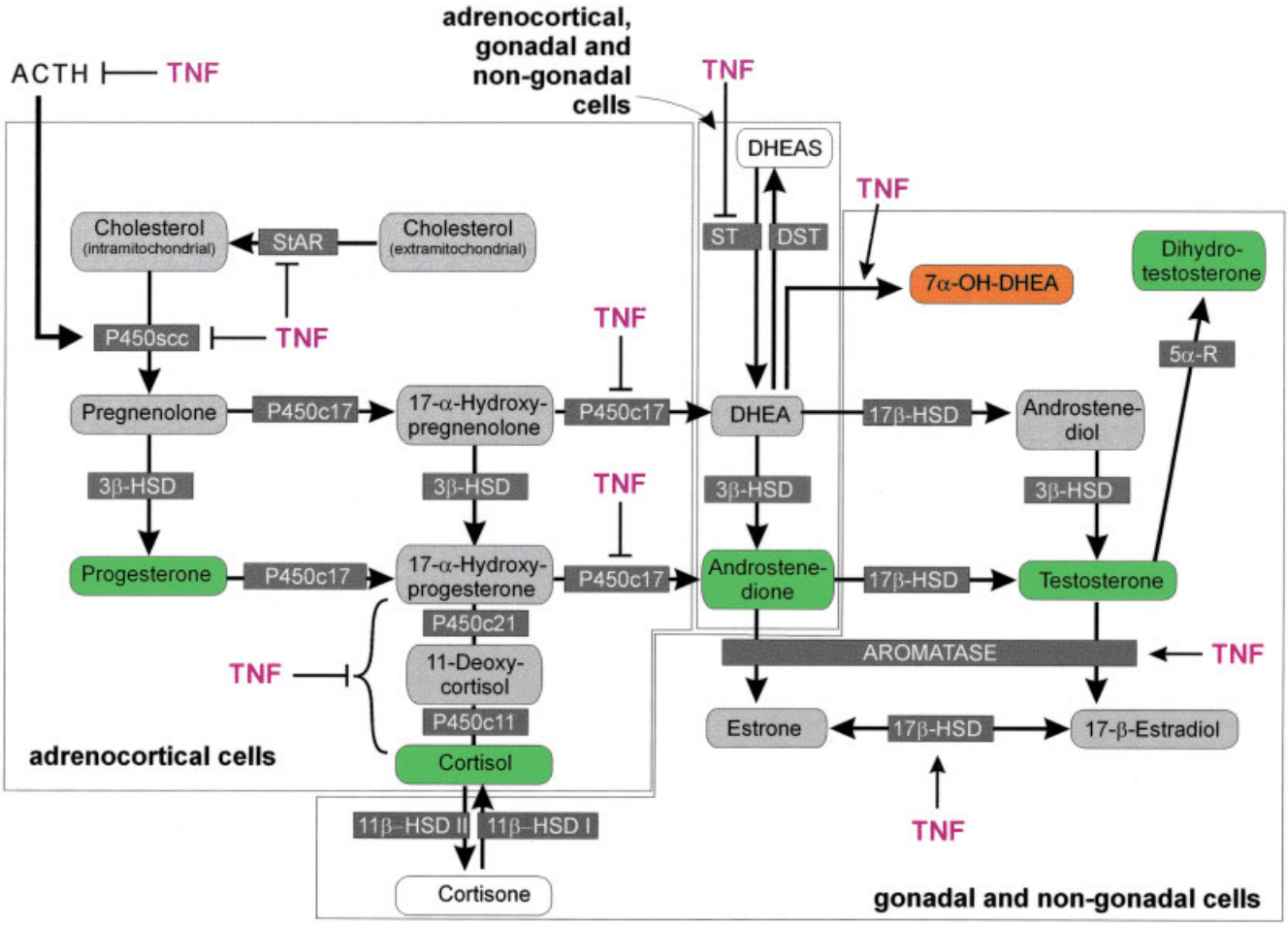

Figure 1. Influence of tumor necrosis factor (TNF) on distinct pathways of steroidogenesis and steroid conversion. Chronically increased serum levels of TNF diminish pituitary secretion of adrenocorticotropic hormone (ACTH). In adrenocortical cells, TNF inhibits the following enzyme steps: P450scc, P450c17, P450c21, and P450c11. In the setting of chronic inflammatory diseases, this leads to an observable preponderance of cortisol at the expense of adrenal or gonadal androgen secretion. In inflamed synovial tissue, TNF inhibits conversion of dehydroepiandrosterone sulfate (DHEAS) to DHEA, stimulates production of 7α-hydroxy-DHEA, and stimulates aromatase. Steroid hormones in red boxes are proinflammatory, and those in green boxes are antiinflammatory. Cortisone and DHEAS (white boxes) are biologically inactive hormones. Arrows indicate a stimulatory effect. Lines with a bar at the end indicate an inhibitory influence. StAR = steroidogenic acute regulatory protein; ST = sulfatase; DST = DHEA sulfotransferase; 5α-R = 5α-reductase; 17β-HSD = 17β-hydroxysteroid dehydrogenase; 3β-HSD = 3β-hydroxysteroid dehydrogenase.

relation to that of the precursor hormone 17α-hydroxyprogesterone and, in addition, in relation to cortisol (15,16). These in vitro and in vivo data indicate that TNF is an important inhibitor of the second step of the P450c17 reaction (Figure 1).

Relative decrease of adrenocorticotropic hormone (ACTH) and cortisol in relation to systemic inflammation

Although ACTH and cortisol levels seem to be relatively normal in patients with RA (17), these levels are low in relation to serum levels of proinflammatory cytokines. This phenomenon has been called inadequate ACTH and cortisol secretion relative to inflammation status (18–24). Tsigos et al reported, in human subjects, dose-dependent increases in ACTH and cortisol levels in association with serum IL-6 levels between 0 pg/ml and 250 pg/ml (25), which demonstrated the normal reaction of the HPA axis on elevated serum cytokine levels. In RA patients with high serum levels of TNF, serum levels of cortisol and androgens are normal or lower than normal, respectively. The reason for this phenomenon is only partly understood, but continuous stimulation of the hypothalamus with proinflammatory cytokines such as TNF or IL-6 in the previously mentioned range

Table 1. Effects of cytokines and growth factors on distinct P450 enzymes of steroidogenesis in vitro*

P450 enzyme/cell type	Cytokine	Effect
StAR		
Leydig	**TNF,** IFNγ, IL-1	**Inhibition**
Ovarian	**TNF**	**Inhibition**
Nongonadal		
Adrenocortical	TGFβ1	Inhibition
P450ssc		
Leydig	**TNF,** IFNγ, IL-1	**Inhibition**
Ovarian granulosa	IL-1	Inhibition
Ovarian theca	TGFβ	Stimulation
3β-HSD		
Leydig	**TNF,** IL-1, bFGF	**Inhibition**
Leydig	EGF	Stimulation
Ovarian granulosa	EGF	Stimulation
Nongonadal		
Breast	IL-3, IL-4	Stimulation
Adrenocortical	TGFβ1	Stimulation
Adrenocortical	EGF	Stimulation
P450c17		
Leydig	**TNF,** IFNγ, IL-1	**Inhibition**
Leydig	TGFβ1	Inhibition
Ovarian granulosa	bFGF, EGF	Inhibition
Nongonadal		
Adrenocortical	TGFβ1	Inhibition
17β-HSD		
Leydig	bFGF	Stimulation
Ovarian	bFGF, IL-6	Stimulation
Ovarian granulosa	TGFβ1	Stimulation
Nongonadal		
Breast (epithelial)	**TNF,** IL-6, IL-8	**Stimulation**
Endometrial cancer	IFNγ	Stimulation
Aromatase		
Ovarian granulosa	TGFβ1, IL-6	Stimulation
Ovarian granulosa	**TNF,** IL-1, EGF, bFGF	**Inhibition**
Nongonadal		
Breast	**TNF,** IL-1, IL-6, IL-11	**Stimulation**
Adipocyte	**TNF,** IL-6, IL-11	**Stimulation**
Adipocyte	EGF	Inhibition
Osteoblast	**TNF,** IL-1, TGFβ1	**Stimulation**
Hepatocyte	TGFβ1	Inhibition
Skin fibroblast	bFGF	Inhibition

* See refs. 69 and 70. The effect of tumor necrosis factor (TNF) is shown in boldface. StAR = steroidogenic acute regulatory protein; IFNγ = interferon-γ; IL-1 = interleukin-1; TGFβ1 = transforming growth factor β1; 3β-HSD = 3β-hydroxysteroid dehydrogenase; bFGF = basic fibroblast growth factor; EGF = epidermal growth factor.

(0–250 pg/ml of IL-6) results in fast hypothalamic–pituitary adaptation, leading to unresponsiveness of these organs (26). In patients with chronic inflammatory diseases such as RA, cytokine levels remain elevated, whereas hormone levels become normal (cortisol) or lower than normal (androgens). Thus, cortisol concentrations remain inadequately low in relation to levels of IL-6 and TNF, and cortisol is unable to decrease production of these cytokines. These lower levels of adrenal hormones are attributable to the direct inhibitory influence of TNF on expression of the steroidogenic acute regulatory protein (Table 1) and on ACTH-stimulated expression of the steroidogenic enzymes P450ssc, P450c21, and P450c11 in adrenocortical cells (Figure 1 and Table 1) (13).

In a recent study, it was demonstrated that immediately after injection of anti-TNF antibodies, an increase in ACTH levels was observed in prednisolone-naive patients with RA (15). ACTH and cortisol levels, in relation to serum TNF levels, continuously increased during 12 weeks of anti-TNF therapy (15,16). Furthermore, the ratio of serum cortisol to serum ACTH decreased during anti-TNF therapy, which indicates sensitization of ACTH secretion with a relative increase in ACTH compared with cortisol (15). It is important to mention that anti-TNF–mediated changes in these hormones are not attributable to changes in serum levels of cortisol-binding globulin (16). In summary, TNF neutralization leads to an improvement of the HPA axis in relation to the proinflammatory situation. This normalization of the milieu interne is an additional important mode of antiinflammatory action.

Intracrinology in synovial tissue

The adrenal and gonadal glands secrete hormones that can be converted to downstream hormones in nongonadal tissue such as the synovium but also in breast cells, adipocytes, osteoblasts, hepatocytes, skin fibroblasts, and others (Table 1). As such, these hormones are prohormones of biologically active sex hormones. For example, in synovial cells, the biologically inactive DHEAS is converted to the biologically active DHEA (27), and DHEA is further converted to 7α-hydroxy-DHEA or 16α-hydroxy-DHEA (28–30). Other hormones, such as androstenedione, testosterone, and 17β-estradiol, are converted to downstream hormones (30), which exert quite different effects on the inflammatory process (represented by different colors in Figure 1) (for review, see ref. 31). Conversion of these prohormones is mediated by available P450-converting enzymes in nongonadal cells, and this conversion is largely influenced by cytokines and growth factors (intracrinology) (Table 1).

In patients with RA, it was recently demonstrated that TNF inhibits conversion of the biologically inactive androgen DHEAS to the active androgen DHEA in synovial cells (27). Neutralization of TNF increased the conversion of DHEAS to DHEA in patients with RA but not in patients with osteoarthritis (27). This can be an important antiinflammatory effect, because TNF neutralization increases the level of the androgen pre-

cursor DHEA (Figure 1). Interestingly, serum levels of DHEA in relation to DHEAS did not increase during anti-TNF therapy in patients with RA (32), which indicates that DHEAS-to-DHEA conversion from noninflamed tissue such as fat tissue may be remarkably higher, which will mask the effects of anti-TNF–induced restoration of local hormone secretion in inflamed synovial tissue.

Dulos et al demonstrated that TNF stimulates the conversion of DHEA to the androgen 7α-hydroxy-DHEA in synovial tissue of RA patients and arthritic animals (Figure 1) (28,29). Other investigators confirmed conversion of this particular steroid hormone in mixed RA synovial cells (30). The 7α-hydroxy-DHEA mediates proinflammatory effects (28,29). One can expect that TNF neutralization inhibits this unfavorable steroid conversion, which, together with the above-mentioned increase of DHEA, would enhance local androgen concentrations.

Furthermore, TNF stimulates the aromatase-mediated conversion of androstenedione to estrone and of testosterone to 17β-estradiol in peripheral nontumor nonendocrine cells (Figure 1 and Table 1) (33,34). Such stimulation would further reduce the availability of antiinflammatory androgens in local tissue. In addition, the increase of estrogens most probably leads to further conversion into downstream pro-proliferative estrogens such as 16α-hydroxyestrogens or 4-hydroxyestrogens (35). This is accompanied by a loss of antimitogenic 2-hydroxyestrogens, as demonstrated in patients with RA and patients with systemic lupus erythematosus (SLE) (36,37).

In this respect, it is interesting that male patients with RA seem to profit more from anti-TNF strategies than do female patients (in Italy, Montecucco CM: personal communication; in Norway, Kvien TK: personal communication). Because male patients have elevated levels of circulating androgens in comparison with female patients, this probably leads to higher local levels of proinflammatory estrogens in men compared with women (e.g., 16α-hydroxyestrogens or 4-hydroxyestrogens). Blockade of TNF-induced up-regulation of aromatase would particularly increase the level of androgens in male as compared with female patients with RA, and this can lead to a better clinical outcome in male patients.

Interestingly, TNF neutralization over several weeks in patients with RA did not change the ratio of serum levels of androgens versus estrogens (32). Several reasons for this obvious discrepancy may exist. First, the neutralizing capacity of anti-TNF therapy in the target tissue is inadequate to restore these hormones. Second, anti-TNF antibodies do not neutralize TNF in the target tissue but influence other important proinflammatory immune phenomena such as apoptosis (38). Third, the amount of adrenal and sex hormones from noninflamed tissue such as fat tissue may be much higher than expected, which can mask the effects of anti-TNF–induced restoration of local hormone secretion in inflamed synovial tissue. Fourth, the hormonal dissociation with an increase in the level of estrogens in relation

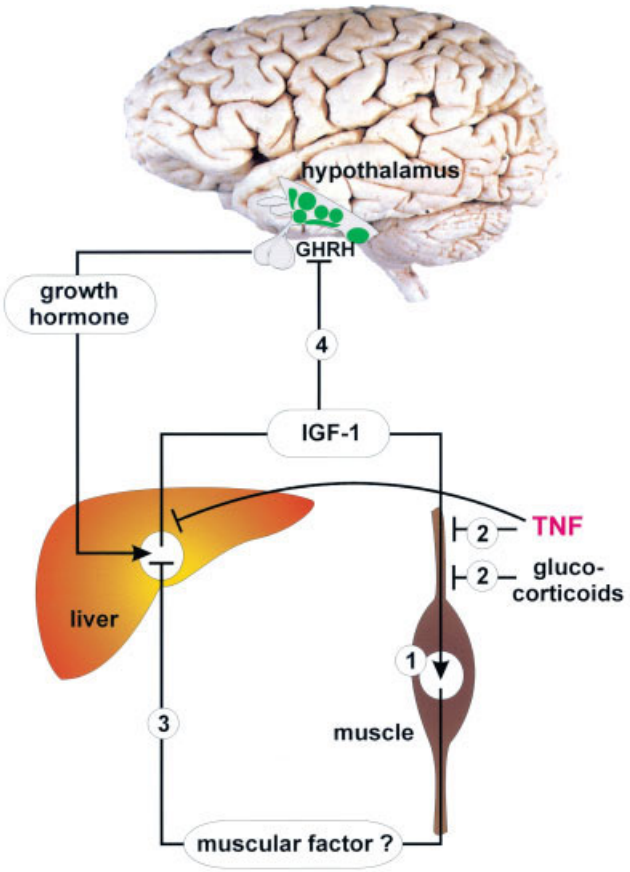

Figure 2. The hypothalamus–pituitary gland–liver–muscle axis. Growth hormone–releasing hormone (GHRH) from the hypothalamus stimulates pituitary growth hormone release. Growth hormone stimulates production of insulin-like growth factor 1 (IGF-1) by the liver. Liver IGF-1 stimulates muscle growth directly and by inducing muscular IGF-1 (**1**). Tumor necrosis factor (TNF) and exogenous glucocorticoids inhibit the effects of liver IGF-1 and local IGF-1 on muscle growth (**2**). TNF and glucocorticoids increase protein degradation in the muscle. Consumption of liver IGF-1 and down-regulation of local IGF-1 decrease the negative feedback signal to the liver (**3**). In patients receiving glucocorticoids, this leads to loss of the negative feedback signal to the liver and, thus, to an increase in measurable liver IGF-1 levels in serum. IGF-1 itself inhibits GHRH release (**4**), which is also inhibited by endogenous and exogenous glucocorticoids.

to androgens lasts for considerably longer than 12–16 weeks, as has been observed previously (39). Fifth, in highly inflamed synovial tissue, TNF is not the sole modulator of altered estrogen production (Table 1). This would imply that neutralization of other cytokines is needed to restore these hormones. Sixth, hormonal alterations may exist for a very long time before the outbreak of RA, which has been demonstrated for serum DHEAS (40). The lack of adequate secretion of important antiinflammatory hormones such as DHEAS can be a genetic prerequisite in an individual affected by RA (40).

The hypothalamus–pituitary gland–liver–muscle axis

A majority of patients with RA experience decreased muscle function and loss of body cell mass (41,42). High levels of TNF in parallel with glucocorticoid therapy were thought to be important elements for these alterations in patients with RA (Figure 2) (43,44). One key element in maintaining muscle mass is the presence of insulin-like growth factor 1 (IGF-1), which promotes muscle growth and suppresses muscle degradation (Figure 2) (45). Glucocorticoid therapy can lead to IGF-1 resistance (46); such resistance has been demonstrated during glucocorticoid therapy by an increase in IGF-1 serum levels (46). A very similar phenomenon exists with respect to insulin resistance (47), and patients with RA demonstrate insulin resistance (48). TNF neutralization improved insulin resistance (48), and anti-TNF therapy improves the HOMA (homeostatis model of assessment) index, which is an indicator of insulin resistance (Li EK: personal communication). Similarly, anti-TNF therapy improves glucocorticoid-induced IGF-1 resistance without influencing myoglobin and IGF-1–binding proteins 1 and 3 (49). These studies demonstrate that TNF neutralization exerts positive effects on insulin and IGF-1 signaling, which is important for overcoming decreased muscle function and reducing cardiovascular risk. These are 2 additional favorable effects of TNF blockade.

The hypothalamus–autonomic nervous system axis

Several studies demonstrated that patients with chronic inflammatory diseases have increased tonus of the sympathetic nervous system (50–53). Increased sympathetic activity is probably closely related to the increased risk of cardiovascular events as observed in patients with RA (54). Such increased sympathetic tonus may be a consequence of relatively decreased serum

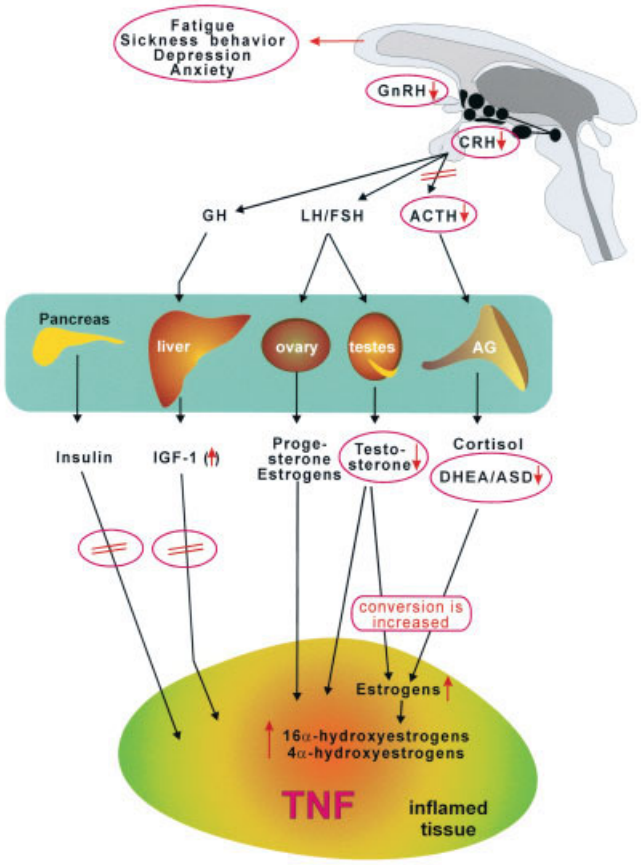

Figure 3. Summary of neuroendocrine alterations in patients with rheumatoid arthritis. Pink circles indicate the deleterious effects of tumor necrosis factor (TNF) on several levels of the endocrine and neuronal supersystems. Double red bars indicate a reduction in the respective pathway. Pathways of the parasympathetic system are not shown. GnRH = gonadotropin-releasing hormone; CRH = corticotropin-releasing hormone; GH = growth hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; ACTH = adrenocorticotropic hormone; AG = adrenal gland; IGF-1 = insulin-like growth factor 1; DHEA = dehydroepiandrosterone; ASD = androstenedione.

levels of cortisol in relation to inflammation, because cooperativity of cortisol and norepinephrine exists on a molecular level via the β-adrenergic receptor signaling cascade (55,56).

Functional loss of one factor probably upregulates the other factor in order to maintain functions such as blood glucose homeostasis, regulation of the bronchial lumen, blood pressure control, and others. Because TNF is relevant for adaptation of the HPA axis, leading to inadequately low cortisol secretion (see above), its neutralization may change the increased sympathetic tonus. In a recent study, we confirmed the

increased sympathetic tonus in patients with RA and also in those with SLE, which was accompanied by a relatively normal tonus of the HPA axis (called "uncoupling of the HPA and HANS axis" during chronic inflammation, because an increase in the tonus of both axes can be expected during acute inflammation) (57). Interestingly, 12 weeks of anti-TNF therapy only slightly decreased the sympathetic tonus as measured by plasma neuropeptide Y levels. Thus, it seems that uncoupling remains for a long time, and it appears that TNF is not the sole and main factor responsible for this phenomenon (i.e., other circulating cytokines are also responsible).

It should be mentioned that increased tonus of the sympathetic nervous system probably would not lead to an increased number of local sympathetic neurotransmitters in the inflamed joint, because sympathetic nerve fibers are lost (58). In such a situation, local concentrations of sympathetic neurotransmitters are too low to exert antiinflammatory effects via β-adrenoceptors (for review, see ref. 59). Whether long-term TNF neutralization increases the density of sympathetic nerve fibers in the synovium is presently not known.

The central nervous system

It is well known that patients with chronic inflammatory diseases show signs of chronic fatigue and depression (60–63). In recent years, it has been demonstrated that circulating cytokines and activation of sensory nerve fibers in the periphery are most probably involved in these central nervous system alterations (64). Cytokines induce so-called sickness behavior (64). The injection of lipopolysaccharide into healthy controls leads to a significant increase in depression scores (65). Further findings demonstrated that elevated cytokine concentrations deteriorate sleep and declarative memory (66). TNF is an important mediator of these changes during the course of chronic inflammatory diseases. Indeed, it has been demonstrated that TNF neutralization decreased sleepiness in patients with sleep apnea (67). In addition, as occurs with patients receiving other immunosuppressive drugs, patients with RA who were receiving anti-TNF antibody therapy demonstrated a marked reduction in fatigue scores (60), and they experienced an improved sense of well-being and decreased joint pain (68). These findings show that elevated levels of circulating TNF have an important impact on brain function.

Conclusion

Numerous hormonal and neuronal pathways are severely altered in patients with RA and those with other chronic diseases (see Figure 3). At several locations, TNF is an important mediator of these alterations (Figure 3). Because TNF is able to modulate many neuroendocrine pathways, most often leading to unfavorable changes of these axes (in the direction of an overall proinflammatory situation), its neutralization is of critical importance to normalize these pathways. Normalization of neuroendocrine axes by anti-TNF therapy supports the antiinflammatory environment and readjusts the milieu interne. Thus, anti-TNF therapy is not only immunosuppressive by inhibiting TNF effects, but it is also favorable in that it restores hormonal pathways, leading to a more normal situation. The described effects of TNF-neutralizing therapies on altered hormonal and neuronal supersystems is an alternative mode of antiinflammatory action. It might well be that neutralization of other cytokines such as IL-1β, IFNγ, or IL-6 can have comparable effects, because these cytokines influence neuroendocrine axes in a similar manner (Table 1). Future studies with cytokine-neutralizing strategies should include hormonal readout parameters in order to further characterize restoration of neuroendocrine axes.

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